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77. (New) A kit for use in a hybridization assay, said kit comprising: an array according to Claim 60.

REMARKS

In view of the amendments made herein and the following remarks, the Examiner is respectfully requested to withdraw all rejections and allow Claims 1-17, 53, and 57-59, as well as newly added Claims 60 – 77, the only claims pending and currently under Examination in this application.

Claims 1, 57 and 58 have been amended to limit the arrays to ones in which each of the oligonucleotide probes in a given probe spot of the array hybridize to the same target nucleic acid. In other words, each probe spot is made up only of a mixture of individual probes that hybridize to the same target nucleic acid. Support for this amendment can be found in the specification at page 15, lines 1 to 10 and page 19, line 12, which teaches that the spots may be produced by mixing the pre-made probes and then placing them on the same location of the array or sequentially placing the individual probes on the same location of the array. Newly introduced Claims 60 to 77 include the additional limitation that the oligonucleotide probes of each of the spots cooperatively hybridize to their target, support for this additional element being found in the specification at page 16, line 23 to page 17, line 13. As such, the above amendments introduce no new matter to the application and their entry by the Examiner is respectfully requested.

Attached hereto is a marked up version of the changes made to the claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."** Also attached is a clean copy of the claims as amendment, which attachment is captioned **"Clean Copy of Complete Set of Amended Claims."**

In the Final Rejection, the rejection of Claims 1, 2, 5-10, 12-17, and 57-58 under 35 U.S.C. § 102 as being anticipated by Brown et al (U.S. Pat. No. 5,807,522) was maintained. In addition, this rejection was maintained in the Examiner's comments in the Advisory

Action, for the asserted reason that the spots as amended to continue to read on the cells disclosed by Brown. In other words, the Examiner continues to read the term "spot" of the presently pending claims as encompassing the disclosed "cell" of the Brown arrays, i.e., the Examiner continues to equate the Brown disclosed microarray of each cell in Brown's multicell array with a spot of the presently claimed arrays.

Initially, it is respectfully submitted that the Examiner is incorrectly equating the spots of the presently claimed arrays with the cells of Brown's multicell arrays. The spots of the presently claimed arrays correspond to Brown's individual regions, i.e. the individual components that make up each of Brown's microarrays. The spots of the present arrays are clearly equal to Brown's regions in view of the specification of the present application, which discloses on page 10, lines 15 to 27, array embodiments that are made of a plurality of oligonucleotide spot patterns, where each oligonucleotide spot pattern is the same as the microarray of Brown. As such, it is respectfully submitted that it is incorrect to equate the probe spots of the claimed arrays with the Brown's cells, as the Examiner has done in maintaining this rejection.

Nevertheless and solely in order to expedite prosecution of the present application to allowance, the arrays have been amended to limit the probe spots of the claimed arrays to ones that are made up of a mixture of individual oligonucleotide probes in which all of the individual oligonucleotide spots are limited to those that hybridize to the same target nucleic acid. This element is found in the claim language which recites that the probe consists of a mixture of a plurality of 2 or more distinct oligonucleotides that hybridize to the same target.

Brown's cells are not a mixture of oligonucleotide probes that all hybridize to the same target. Instead, Brown's cell is a microarray of individual probes each positioned as a defined location and not present as a mixture. This format of Brown's cell is critical since Brown's cell is a microarray. If the cell were just a mixture of the probes which means that the probes are positioned at defined locations, Brown's cell would not be a microarray. Furthermore, since Brown's cell is a microarray, one of skill in the art would read this as teaching a microarray of probes that hybridize to different targets, not the same target.

Therefore, the probe spots of the claimed arrays are clearly not the same as the cells of Brown's arrays.

In sum, Claims 1, 2, 5-10, 12-17, and 57-58, which require each oligonucleotide spot to be a mixture of different oligonucleotide probes that all hybridize to the same target nucleic acid are not anticipated by Brown et al. because Brown does not teach this limitation. Accordingly, Claims 1, 2, 5-10, 12-17, and 57-58, as well as newly added Claims 60 to 77, are not anticipated under 35 U.S.C. § 102 over Brown and this rejection may be withdrawn.

Claims 3-4 were rejected under 35 U.S.C. § 103(a) over Brown et al in view of Fodor et al. (U.S. Pat. No. 5,800,992, filed June 25, 1996) for the asserted reason that Brown teaches all of the limitations of the claimed invention except for the placement of the probes on the array corresponding to non-overlapping or overlapping regions of a target nucleic acid, which is assertedly supplemented by the Fodor et al. reference.

The M.P.E.P. teaches that a proper *prima facie* case requires that a combined teaching of two or more references must teach or suggest all the claim limitations. The M.P.E.P. states in relevant part:

> "To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. **Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.**" M.P.E.P. § 2142.

Thus, in order for a proper *prima facie* case to made, the combined teachings of the cited references must teach or suggest all of the limitations of the claims.

In the present application, the Applicants are claiming an array which is limited in that each polynucleotide probe spot must be a mixture of oligonucleotides that all hybridize to the same target.

As demonstrated above, Brown fails to teach or suggest an array in which each spot must contain a mixture of two or more different oligonucleotides of different sequence that hybridize to the same nucleic acid target since Brown's cells are not mixtures of different oligonucleotides that all hybridize to the same target.

For the following reasons, Fodor fails to make up this fundamental deficiency in the Brown reference. Fodor teaches that "probes of known . . . sequence may be immobilized to the matrix and a map of **various different target sequences** may be determined from overlaps." (Col. 10, lines 9-12). Thus, Fodor suggests using probes to map or determine the sequential ordering of a plurality of various sequences using probes that hybridize to various different target sequences. In other words, different probe spots on the Fodor array may include probes that hybridize to different regions of the same target nucleic acid sequence. **However, each probe spot on the Fodor array is made up of identical probes, not two or more different probes of different sequence.** As such, Fodor fails to make up the fundamental deficiency in the Brown teaching.

As such, the combined teachings of the cited references fail to teach or suggest an array of probe oligonucleotide spots where each spot contains a plurality of unique oligonucleotides of different sequence that each hybridize to the same target nucleic acid and each spot is a mixture of the oligonucleotide probes. Because this limitation of the claimed invention is neither taught nor suggested by the combined teachings of the cited references, a proper *prima facie* case of obviousness has not been established.

In sum, because the combined teachings of Brown and Fodor fail to teach or suggest an array on which each oligonucleotide probe spot contains a plurality of unique polynucleotide probes containing two or more different probes of different sequence that hybridize to the same target nucleic sequence and the spot is a mixture of the oligonucleotide

probes, Claims 3-4 are not obvious under 35 U.S.C. § 103(a) over these references and this rejection may be withdrawn.

Claims 11 was rejected under 35 U.S.C. §103(a) over Brown in view of a Lockhart et. al. (U.S. Pat. No. 6,040,138, filed June 7, 1995) for the asserted reason that Brown teaches the array of the present invention but for the element of at least one mismatch probe on the array, which this missing element is provided by the Lockhart reference. However, as demonstrated above, the Brown fails to teach or suggest the fundamental limitation that each probe spot be made up solely of a mixture of at least two different oligonucleotides of different sequence that hybridize to the same target nucleic acid. As Lockhart is cited solely for his teaching of mismatch probes, this reference fails to make up this fundamental deficiency of Brown. Accordingly, Claim 11 is not obvious over Brown in view of Lockhart and this rejection may be withdrawn.

Finally, Claims 53 and 59 have been rejected under 35 U.S.C. §103(a) over Brown et al. in view of a Stratagene catalog (1988), page 39 for the asserted reason that Brown teaches arrays of the claimed invention (i.e. the array according to Claim 1) but for the motivation to combine reagents with the array to make up the kit, which missing element is provided by the Stratagene reference. However, as demonstrated above, the Brown reference fails to teach or suggest the fundamental limitation that each probe spot contain at least two different oligonucleotides of different sequence that hybridize to the same target nucleic acid, where the probe spot is a mixture of the oligonucleotides. As the Stratagene reference is cited solely for the teaching of kits in general, this reference fails to make up this fundamental deficiency of Brown. Accordingly, Claims 53 and 59 are not obvious over Brown in view of Stratagene and this rejection may be withdrawn.

In view of the attached amendments and remarks, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Date: 3·16·01

By: _____
Bret Field
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encs:

- Marked up Copy of Amended Claims
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) An array comprising at least one pattern of probe oligonucleotide spots stably associated with the surface of a solid support, wherein each probe oligonucleotide spot [comprises an oligonucleotide probe composition made up] consists of a mixture of a plurality of [unique oligonucleotides, wherein said plurality comprises] 2 or more unique oligonucleotides of different sequence that hybridize to the same target nucleic acid.

2. The array according to Claim 1, wherein said plurality of unique oligonucleotides hybridize to different regions of said target nucleic acid.

3. The array according to Claim 2, wherein said plurality of unique oligonucleotides hybridize to non-overlapping regions of said target nucleic acid.

4. The array according to Claim 2, wherein said plurality of unique oligonucleotides hybridize to overlapping regions of said target nucleic acid.

5. The array according to Claim 1, wherein two or more different target nucleic acids are represented in said pattern.

6. The array according to Claim 5, wherein each probe oligonucleotide spot in said pattern corresponds to a different target nucleic acid.

7. The array according to Claim 5, wherein two or more probe oligonucleotide spots in said pattern correspond to the same target nucleic acid.

8. The array according to Claim 1, wherein said array comprises a plurality of said patterns.

9. The array according to Claim 8, wherein said plurality of patterns are separated from each other by walls.

10. The array according to Claim 1, wherein each of said oligonucleotides ranges from about 15 to 150 nucleotides in length.

11. The array according to Claim 1, wherein said array further comprises at least one mismatch probe.

12. (Amended) The array according to Claim 1, wherein [each of said oligonucleotide probe compositions] said plurality ranges from about 3 to 50 oligonucleotides in number.

13. The array according to Claim 1, wherein all of said oligonucleotide spots correspond to the same type of target nucleic acid.

14. The array according to Claim 1, wherein the spots on said array do not exceed a density of about $1000/cm^2$.

15. The array according to Claim 14, wherein the spots on said array do not exceed a density of about $400/cm^2$.

16. The array according to Claim 1, wherein the spots on said array range from about 50 to 10,000 in number.

17. The array according to Claim 1, wherein the spots on said array range from about 50 to 1,000 in number.

53. A kit for use in a hybridization assay, said kit comprising:
an array according to Claim 1.

57. (Amended) An array comprising a pattern of probe oligonucleotide spots, wherein each probe oligonucleotide spot comprises an oligonucleotide probe composition [made up] consisting of a mixture of 3 to 50 unique oligonucleotides of different sequence and from about 15 to 150 nucleotides in length that hybridize to the same target nucleic acid, wherein each unique oligonucleotide hybridizes to a different region of said target nucleic acid of the probe oligonucleotide spot.

58. (Amended) An array comprising a pattern of probe oligonucleotide spots of a density that does not exceed about 400 spots/cm^2, wherein each probe oligonucleotide spot [comprises an oligonucleotide probe composition made up] consists of a mixture of 3 to 20 unique oligonucleotides of different sequence and from about 25 to 100 nucleotides in length that hybridize to the same target nucleic acid, wherein each unique oligonucleotide hybridizes to a different region of the said target nucleic acid.

59. The kit according to Claim 53, wherein said kit further comprises reagents for generating a labeled target nucleic acid sample.

Please add the following new claims:

--60. (New) An array comprising at least one pattern of probe oligonucleotide spots stably associated with the surface of a solid support, wherein each probe oligonucleotide spot consists of a mixture of a plurality of 2 or more unique oligonucleotides of different sequence that cooperatively hybridize to the same target nucleic acid.

61. (New) The array according to Claim 60, wherein said plurality of unique oligonucleotides hybridize to different regions of said target nucleic acid.

62. (New) The array according to Claim 61, wherein said plurality of unique oligonucleotides hybridize to non-overlapping regions of said target nucleic acid.

63. (New) The array according to Claim 61, wherein said plurality of unique oligonucleotides hybridize to overlapping regions of said target nucleic acid.

64. (New) The array according to Claim 60, wherein two or more different target nucleic acids are represented in said pattern.

65. (New) The array according to Claim 64, wherein each probe oligonucleotide spot in said pattern corresponds to a different target nucleic acid.

66. (New) The array according to Claim 64, wherein two or more probe oligonucleotide spots in said pattern correspond to the same target nucleic acid.

67. (New) The array according to Claim 60, wherein said array comprises a plurality of said patterns.

68. (New) The array according to Claim 67, wherein said plurality of patterns are separated from each other by walls.

69. (New) The array according to Claim 60, wherein each of said oligonucleotides ranges from about 15 to 150 nucleotides in length.

70. (New) The array according to Claim 60, wherein said array further comprises at least one mismatch probe.

71. (New) The array according to Claim 60, wherein said plurality ranges from about 3 to 50 oligonucleotides in number.

72. (New) The array according to Claim 60, wherein all of said oligonucleotide spots correspond to the same type of target nucleic acid.

73. (New) The array according to Claim 60, wherein the spots on said array do not exceed a density of about $1000/cm^2$.

74. (New) The array according to Claim 73, wherein the spots on said array do not exceed a density of about $400/cm^2$.

75. (New) The array according to Claim 60, wherein the spots on said array range from about 50 to 10,000 in number.

76. (New) The array according to Claim 60, wherein the spots on said array range from about 50 to 1,000 in number.

77. (New) A kit for use in a hybridization assay, said kit comprising:
an array according to Claim 60. --